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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,442	02/10/2004	Moses Rodriguez	2609/60726-AZ/JPW/GJG/DJK	3701

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John P. White
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036

EXAMINER	
WANG, CHANG YU	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 03/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/776,442	RODRIGUEZ ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-42,44 and 45* is/are pending in the application.

4a) Of the above claim(s) *19-27,44 and 45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/07/05,12/03/04,*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

02/10/04, 11/12/04

DETAILED ACTION

Status of Application/Election/Restrictions

1. Applicant's election with traverse of Group II and multiple sclerosis for the species election of disease in the reply filed January 9, 2006 is acknowledged. The traversal is on the ground(s) that the methods in Groups I-II and IV are related because these methods use an antibody against an epitope on glatiramer acetate. In addition, Applicant argues that the examination/search of Groups I-IV would not be a serious search burden on the examiner. This is not found persuasive because the steps and patients required in the method of treating diseases associated with demyelination of the central nervous system by administering an antibody against glatiramer acetate are not required in the methods of stimulating remyelination (Group I) or lymphocyte proliferation (Group IV) in vitro or in vivo. In addition, the outcomes in the method of treatment are not the same as in the methods of stimulating remyelination or lymphocyte proliferation in vitro or in vivo. The patient populations, steps and outcomes are different among these different Groups, indicating that the search is not co-extensive. A reference to one element would not constitute a reference to another.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 19-42, 44 and 45 are pending. Claims 19-27, 44 and 45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Groups I, III-IV, there being no allowable generic or linking claim. In addition, claims 39

and 40 are also withdrawn from further consideration because of non-elected species. Claims 28-38, 41 and 42 are under examination in this office action.

Priority

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Claim Objections

4. Claim 38 is objected to as encompassing non-elected subject matter.

5. Applicant is advised that should claim 34 be found allowable, claim 35 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 28-38, 41 and 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for stimulating remyelination in an experimental mouse model of multiple sclerosis induced by Theiler's murine encephalomyelitis virus (TMEV) by administering anti-glatiramer acetate IgG, does not reasonably provide enablement for treating a subject suffering from all diseases associated with demyelination of central nervous system by administering an antibody that binds all types of epitopes on glatiramer acetate as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

8. "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'. These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)". See MPEP § 2164.01.

The claims are drawn to a method of treating a subject suffering from a disease associated with demyelination of the central nervous system axon by administering an antibody against glatiramer acetate. The instant specification discloses that passively immunizing the TEMV induced mice, which is one of multiple sclerosis animal models, with anti-glatiramer acetate IgG can enhance olgodendrocyte remyelination in these TEMV induced mice. Applicant also discloses that cells stained with anti-glatiramer acetate antibody in the spinal cord histochemical staining are A2B5 or O-1 negative cells, suggesting that the anti-glatiramer acetate antibody is not cross-reactive with oligodendrocytes. However, Applicant fails to provide enough guidance as to how to use the findings from the TEMV mouse model in treating all diseases associated with demyelination. Based on MeSH databases of the National Library of Medicine, the diseases associated with demyelination at least include demyelinating autoimmune diseases (which including diffuse cerebral sclerosis of Schilder encephalomyelitis, autoimmune experimental leukoencephalitis, multiple sclerosis, myelitis, and neuromeylitis optica), and hereditary central nervous system diseases (which including Adrenoleukodystrophy, Alexander disease, Cananvan disease, leukodystrophy, and Pelizaeus-Merzbacher disease). The cause of each disease is very different from each other and probably is still unclear either. For example, in demyelinating autoimmune

diseases, multiple sclerosis (MS) is an autoimmune disorder mainly affecting young adults and characterized by destruction of myelin in the central nervous system and its pathologic findings include demyelination throughout the white matter of the central nervous system. One of the potential mechanisms for MS is that it is an autoimmune disease of TH-1 type cell mediated immune response to myelin sheath, which subsequently results in inflammation and degeneration in the nervous system. In hereditary central nervous system diseases, Pelizaeus Merzbacher Disease is a rare, slowly progressive disorder of myelin formation and its classic form is X-chromosome linked. Its onset is in infancy and associated with a mutation of the proteolipid protein gene. Its pathologic features are perivascular island-like demyelination in white matter. Since Applicant has provided no guidance in applying the findings of the TEMV mouse model in treating all forms of demyelinating diseases, it is unpredictable whether administering anti-glatiramer acetate IgG is able to treat all demyelinating diseases, indicating that undue experimentation is required.

In addition, in the example of autoimmune demyelinating diseases, the pathology of MS is very heterogeneous. It has been shown that at least four different patterns of pathology in MS. Patterns I and II can be shown close similarity in the animal model of experimental autoimmune encephalomyelitis (EAE), where the lesions are induced by autoreactive T cells and autoantibodies (see p. 375, first paragraph, 't Hart et al. Curr. Opin. Neurol. 2003. 16: 375-383). 't Hart et al. also showed that the animal models for MS can not truly reflect the pathogenic mechanisms of MS. Each animal model has the partial clinical aspects and histopathology of MS, indicating that the effects shown in

one MS mouse model does not truly reflect the end results in patients with different forms of MS. This scenario also applies to the instant MS mouse model induced by TEMV (see p. 377, 't Hart et al. Curr. Opin. Neurol. 2003. 16: 375-383). Although it has been shown that injection of MBP into mice can induce experimental allergic encephalomyelitis (EAE), which subsequently initiates a cascade of immune-mediate damages, the cause of MS is still not established. Since the prior art has not deciphered the cause of all forms of MS, it is very difficult to predict whether passive immunizing with anti-glatiramer acetate antibody can achieve the goal of treating the disease. Without knowing its full scope of etiology and molecular mechanisms in MS, whether the administration of anti-glatiramer acetate antibody can treat MS is unpredictable, indicating that undue experimentation is required for one of ordinary skill in the art to use the invention.

Furthermore, glatiramer acetate is a random copolymer of four amino acids glutamate, tyrosine, alanine and lysine that mimics myelin basic protein (MBP). Applicant fails to disclose and is not in possession of anti-glatiramer acetate antibodies that can recognize all epitopes on glatiramer acetate. Since glatiramer acetate is a random copolymer of the amino acids as stated in the specification (p.5 line 21 to p. 6 line 9), the conformation of any length of amino acids with at least three amino acids can form an epitope. The instant specification has not disclosed sufficient information as the anti-glatiramer acetate antibody possessed by Applicant can bind to all epitopes on glatiramer acetate. Moreover, Applicant has not provided any guidance as to use nonhuman antibodies to treat the diseases. It has been known in the art that human

develop anti-mouse antibodies in immunotherapeutic approaches, which subsequently results in a lot adverse effects. Applicant has not taught how to use nonhuman antibodies in treating demyelinating diseases, indicating that undue experiment is required for a skilled artisan to practice the invention.

The instant specification has not enabled one of skill in the art to use the anti-glatiramer acetate antibody to treat all diseases associated with demyelination of centeral nervous system axon, which are caused by all possible mechanisms. Therefore, it will still require tremendous efforts and undue experimentation to decipher the cause of all forms of demyelinating diseases first and further provide enough guidance for one of ordinary skill in the art to use the method to potentially treat these diseases. Since the cause of the disease is still unknown and the outcomes of the treatment using the claimed method are unpredictable, the artisan would require further guidance to use the claimed method to treat all demyelinating diseases with an expectation of success.

9. Therefore, in view of the breath of claims, the necessity of experimentation, the limited working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention as it pertains to a method for treating a subject suffering from a disease associated with demylination of central nervous system. Undue experimentation would indeed be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The language "consists essentially of" is usually used for a composition and denotes that the composition contains no additional ingredients that materially affect the properties of the composition. It is unclear how a specific antibody molecule can comprise additional ingredients which do not change its properties.

11. Claims 34 and 35 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant has not sufficiently described a macrophage and microglial phenotype so that a skill artisan knows what is encompassed, which renders the claims indefinite.

The term " primarily reacts " in claims 34 and 35 is a relative term which renders the claim indefinite. The term " primarily reacts " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The phrase "primarily reacts" is one of degree which makes the claim indefinite because the requisite degree of reaction is not defined.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 28, 30-38, 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over either of Rodriguez et al. (U.S. Patent 5, 591, 629 issued on Jan 7, 1997 as in IDS submitted Feb 10,2004) or Warrington et al. (Proc. Natl. Acad. Sci. USA. June 6, 2000. 97:6820-6825) in view of Arnon et al. (U.S. Patent No. 6214791 issued on Apr 10, 2001 as in IDS submitted Dec 03, 2004) and Teitelbaum et al. (Pro. Natl. Acad. Sci. USA 1991, 88: 9528-9532).

14. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

U.S. Patent 5,591,629 teaches that an IgM monoclonal antibody SCH94.03 is able to promote CNS remeylination in one of the MS mouse models induced by infection of TEMV (see columns 5-7). The SCH94.03 is an antibody raised against spinal cord homogenates, which contain glial cells and myelin antigens, such as myelin basic protein (MBP) and proteolipid protein (PLP). US

Patent 5591629 fails to teach using an anti-glatiramer acetate IgG to treat a MS model induced by TEMV.

Warrington et al. teach that human polyclonal and monoclonal IgM and IgG are able to promote oligodendrocyte remyelinaiton in the MS mouse model induced by infection of TEMV (see p. 6821, first column. Human antibodies and their isolation; p. 6823, first column, Human mAbs that binds to Ols promote CNS remyelination in TMEV-infected mice). Warrington et al. fail to teach using anti-glatiramer acetate IgG to promote remyelination

U.S. Patent No. 6214791 teaches using Copolymer 1/glatiramer acetate as a therapeutic agent through ingestion or inhalation to treat multiple sclerosis (see column7 Example 3).

Teitelbaum et al. teach that most monoclonal anti-glatirmer antibodies do not cross-react with myelin basic protein and only some monoclonal anti-glatiramer acetate antibodies cross react with MBP (see p. 9531, first column, second paragraph). However, one third of anti-MBP antibodies are cross reactive with glatiramer acetate, which is one of few drugs approved to treat multiple sclerosis (see p. 9528, abstract). Teitelbaum et al. further teach that glatiramer acetate may compete with the binding of MBP to the major histocompatibility complex and subsequently affect the autoimmune response to MBP (see p. 9528, first column, second paragraph).

It would have been obvious for one of ordinary skill in the art at the time of the instant invention was made to combine the teachings of either of U.S. Patent

5,591,629, or Warrington et al., U.S. Patent No. 6214791, with Teitelbaum et al. to administer an antibody against an epitope on glatiramer acetate in promoting remyelination in the MS mouse model induced by TEMV. The person of ordinary skill in the art would have been motivated to make those modifications because glatiramer acetate has been shown to activate T cell activity and subsequently protect nerve cells from toxicity. In addition, the anti-glatiramer acetate antibody has been shown to either cross react or not cross react with MBP and the antibody SCH94.03 against spinal cord homogenates has been shown to promote remyelination in MS mouse animal model induced by TEMV. Therefore, one of ordinary skill in the art would have expected success in promoting oligodendrocyte remeylination in MS animal model induced by TEMV by administering an anti-glatiramer acetate antibody, which is not cross reactive with MBP or oligodendrocytes, in the test animals.

Conclusion

NO CLAIM IS ALLOWED.

15. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

16. Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang, Ph.D. whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867.

18. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CYW
February 23, 2006

Brenda Brumback

BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600